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Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback

Keely A. Muscatell [a,*], Mona Moieni [b], Tristen K. Inagaki [c], Janine M. Dutcher [b], Ivana Jevtic [b], Elizabeth C. Breen [d,e], Michael R. Irwin [b,d,e], Naomi I. Eisenberger [b,*]

[a] Department of Psychology, University of California, Berkeley, United States
[b] Department of Psychology, University of California, Los Angeles, United States
[c] Department of Psychology, University of Pittsburgh, United States
[d] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, United States
[e] Cousins Center for Psychoneuroimmunology, University of California, Los Angeles, United States

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ABSTRACT

Inflammation, part of the body's innate immune response, can lead to "sickness behaviors," as well as alterations in social and affective experiences. Elevated levels of pro-inflammatory cytokines have been associated with increased neural sensitivity to social rejection and social threat, but also decreased neural sensitivity to rewards. However, recent evidence suggests that inflammation may actually enhance sensitivity to certain social rewards, such as those that signal support and care. Despite a growing interest in how inflammation influences neural reactivity to positive and negative social experiences, no known studies have investigated these processes in the same participants, using a similar task. To examine this issue, 107 participants were randomly assigned to receive either placebo or low-dose endotoxin, which safely triggers an inflammatory response. When levels of pro-inflammatory cytokines were at their peak, participants were scanned using fMRI while they received positive, negative, and neutral feedback from an "evaluator" (actually a confederate) about how they came across in an audio-recorded interview. In response to negative feedback (vs. neutral), participants in the endotoxin condition showed heightened neural activity in a number of threat-related neural regions (i.e., bilateral amygdala, dorsal anterior cingulate cortex) and a key mentalizing-related region (i.e., dorsomedial PFC), compared to placebo participants. Interestingly, when receiving positive feedback (vs. neutral), endotoxin (vs. placebo) led to greater neural activity in the ventral striatum and ventromedial PFC, regions often implicated in processing reward, as well as greater activity in dorsomedial PFC. Together, these results reveal that individuals exposed to an inflammatory challenge are more "neurally sensitive" to both negative and positive social feedback, suggesting that inflammation may lead to a greater vigilance for both social threats and social rewards.

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1. Introduction

As part of the innate immune system, the inflammatory response, our "first line of defense" against foreign agents, is critical not only for protecting the body against injuries and infections, but also for altering behavior during times of illness. Specifically, pro-inflammatory cytokines can act on the brain to induce "sickness behavior," a constellation of symptoms including loss of appetite, fatigue, achiness, and fever, which are thought to promote recovery and recuperation during illness and infection (Dantzer and Kelley, 2007). Indeed, a peripheral increase in levels of cytokines in the body can induce central cytokines in the brain, which can then influence neural reactivity and sickness behaviors (Dantzer et al., 2008). In the past decade, it has been demonstrated that inflammation can alter social and affective experiences as well, presumably also an adaptive response to maximize recovery from illness (Dantzer et al., 2008; Raison et al., 2006). In other words, in addition to the physical symptoms we typically think of as accompanying sickness, the inflammatory response also leads to a cascade of psychological changes that are just beginning to be fully explored.

* Corresponding authors at: Department of Psychology, UC Berkeley, 4143 Tolman Hall MC 5050, Berkeley, CA 94720-5050, United States (K. Muscatell). Department of Psychology, UCLA, 1285 Franz Hall Box 951563, Los Angeles, CA 90095-1563, United States (N. Eisenberger).

E-mail addresses: kmuscatell@berkeley.edu (K.A. Muscatell), neisenbe@ucla.edu (N.I. Eisenberger).

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Prior research suggests that increases in pro-inflammatory cytokines are associated with greater depressed mood (Eisenberger et al., 2010b; Harrison et al., 2009; Reichenberg et al., 2001), heightened feelings of social disconnection (Eisenberger et al., 2010b; Moieni et al., 2015b), greater neural sensitivity to social rejection (Eisenberger et al., 2009) as well as more general social threat (Inagaki et al., 2012). These results make sense from an evolutionary perspective: When in a vulnerable state due to infection or injury, the ability to identify threatening individuals in the environment who may pose additional harm would be adaptive, and thus the brain may be "primed" to activate the "neural alarm system" (Eisenberger and Lieberman, 2004) in response to cues of potentially threatening conspecifics.

Less is known about the effects of an inflammatory response on neural responses to *positive* experiences. Two studies suggests that increases in levels of pro-inflammatory cytokines are associated with decreased neural sensitivity in reward-related neural regions in response to monetary rewards (Capuron et al., 2012; Eisenberger et al., 2010a). These findings are consistent with animal research suggesting that inflammation leads to decreased consumption of palatable foods and lower likelihood of engaging in sexual behavior (de la Garza, 2005), as well as lower levels of activity in reward-related neural regions (Stone et al., 2006). This cytokine-induced "anhedonia" may also play an adaptive role during times of sickness, leading the organism to rest and recuperate rather than seeking out pleasurable stimuli that may serve to further weaken an already compromised physical condition.

However, recent findings have also shown that inflammation can sometimes lead to *increases* in reward processing, such as when viewing images of support givers (Inagaki et al., 2015) or when given the opportunity to affiliate with a familiar cage-mate (Yee and Prendergast, 2010). Greater sensitivity to "social rewards" during times of sickness may also serve an adaptive function, perhaps because individuals who mean to help or provide support are especially useful when one is in a vulnerable state (Cole, 2006; Hennessy et al., 2014). Yet, it is unclear if greater neural sensitivity to social rewards during sickness is specific to close-others, or if it is a more generalized response to other sources of positive social information. Hence, the present study aimed to examine how an inflammatory challenge alters neural sensitivity to negative and positive social feedback, in the same group of participants, and using similar tasks.

To accomplish this goal, we conducted a double-blind, placebo-controlled trial comparing neural responses to social feedback among individuals exposed to endotoxin (which safely triggers an increase in pro-inflammatory cytokines) vs. those in a typical inflammatory state (i.e., placebo). Consistent with prior work, we hypothesized that endotoxin (vs. placebo) would lead to greater neural activity in brain regions that respond to threat and pain (i.e., dACC, amygdala, anterior insula) during negative social feedback (relative to neutral). We also examined how endotoxin (vs. placebo) affected activity in reward-related neural structures (i.e., ventral striatum, ventromedial prefrontal cortex [VMPFC]) during positive social feedback (compared to neutral). In addition, because the dorsomedial prefrontal cortex (DMPFC) is important for understanding the mental states of others (which is critical for a task in which one is being evaluated by others), and because there is increasing interest in evaluating the social cognitive impacts of the inflammatory response (Kullmann et al., 2014; Moieni et al., 2015a), we also examined how endotoxin altered DMPFC activity in response to receiving both positive and negative feedback. Finally, we explored if, in addition to affecting neural responses, exposure to endotoxin was associated with self-reported affective responses to the social feedback.

2. Method

2.1. Participants

One hundred fifteen healthy participants (69 females; *M* age = 24.17, *SD* = 6.61) completed the study, as previously described (Inagaki et al., 2015; Moieni et al., 2015a,b). Sixty-one participants were randomly assigned to receive low-dose endotoxin (0.8 ng/kg of body weight), while 54 were randomly assigned to receive placebo (0.9% saline), both administered by a nurse through intravenous bolus. All participants met common inclusion criteria for fMRI studies (i.e., no claustrophobia, current pregnancy, or metal implants), and were also confirmed to be free of Axis-I psychiatric conditions (via the SCID) as well as current physical health issues (i.e., allergies, autoimmune disease, BMI greater than 30, current prescription or recreational drug use). Of the 115 participants who completed overall study procedures, five did not complete fMRI scanning (two due to extreme sickness responses to the endotoxin, one due to claustrophobia, one due to a previously-unreported metallic implant, and one due to scanner technical issues), two had incomplete or unusable fMRI data (due to technical issues with stimulus presentation), one participant (from the endotoxin condition) was excluded from all fMRI analyses for being an outlier (more than 3 SD below the mean) on activity in multiple ROIs for contrasts of both negative and positive feedback, one participant (from the endotoxin condition) was excluded from correlation analyses involving IL-6 for being an outlier (more than 3 SD below the mean), and three participants (from the endotoxin condition) were excluded from correlation analyses involving TNF-α for being outliers (more than 3 SD below the mean). Thus, we had a final sample of 107 participants with usable fMRI data (endotoxin: $n = 56$; placebo: $n = 51$), 106 participants with both usable fMRI and plasma IL-6 data (endotoxin: $n = 55$), and 104 participants with both usable fMRI and plasma TNF-α data (endotoxin: $n = 53$). All participants provided written informed consent, and the UCLA IRB approved all study procedures. The study was registered as a Clinical Trial (#NCT01671150).

2.2. Procedures

Complete details of the overall study procedures are described elsewhere (Moieni et al., 2015a,b) but are summarized here. Participants completed both telephone and in-person screening sessions to confirm they met the eligibility criteria described above. On the day of the experimental session, participants arrived at the UCLA Clinical and Translational Research Center (CTRC), where a nurse inserted a catheter into the dominant forearm for hourly blood draws and a catheter into the non-dominant forearm for continuous saline flush and drug administration. During a 90-min acclimation period, participants completed an audio-recorded interview in which they were asked questions about themselves for approximately 10 min (e.g., "What is your best quality?," and "What are you most afraid of?"). Participants were told that, during the MRI scan, trained evaluators would listen to and evaluate their interview. After the 90 min acclimation period, participants received either the endotoxin or placebo injection, and approximately 2 h later (when the inflammatory response begins to peak for those in the endotoxin condition; Eisenberger et al., 2009, 2010a,b; Moieni et al., 2015a,b), participants underwent an fMRI scan during which they received feedback on their interview from an evaluator (see "Social Feedback fMRI Task" section below for more details), among other neuroimaging tasks not reported here (see Inagaki et al., 2015). Hourly blood draws were taken throughout the session to assess levels of pro-inflammatory cytokines (at baseline prior to endotoxin/placebo administration and then approximately every hour after

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